REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Since the Examiner objects to Claim 8 due to the recitation of nonelected subject matter, the present amendment has deleted the nonelected antigenic subunit of avian hepatitis E virus ("HEV") of Claim 8(d) in compliance with the Examiner's requirement to correct the claim. Also, to advance prosecution towards an allowance, the withdrawn Claims 4, 5, 7 and 17-20 are now canceled with the understanding that Applicants' maintain their right to file a divisional application directed to the nonelected subject matter of this invention in due course.

The Examiner rejects Claims 3, 6, 8, 14, 15, 19 and 20 under 35 U.S.C. § 112, second paragraph, for reasons set forth in the Office action on pages 2-4. Without comment on the merits of this rejection but to expedite matters, Applicants have rewritten the claims for the better readability thereof. Since it is believed that the amendment will overcome the rejection, Applicants respectfully request that the rejection be withdrawn.

Should any further amendment be deemed warranted by the Examiner to place this application in condition for an allowance, she is invited to contact the undersigned attorney in order to discuss the Examiner's recommendations for any proposed revisions.

The Examiner rejects Claims 8-13 under 35 U.S.C. § 112, first paragraph, as failing to provide enablement for a vaccine comprising an isolated avian hepatitis E virus ("HEV") that confers protection against a viral infection or disease, or for a method of vaccination using such a vaccine, or for the nucleic acid vaccine as previously recited in Claim 8(e) for reasons set forth in the Office action on pages 5 and 6. In view of the present amendment, Applicants' proffered evidence of record and the following reasons, Applicants respectfully ask that the Examiner kindly reconsider the patentability of Claims 8-13.

As previously pointed out, the working examples do demonstrate that avian HEV is antigenically related to Sar-55 human HEV and swine HEV (see the paragraph bridging pages 15 and 16, and Example 18 on pages 52 and 53). In Western blot analysis illustrated in Example 18, the purified truncated ORF2 protein of avian HEV reacted with the antiserum obtained from chickens experimentally infected with avian HEV but not with sera from normal control chickens. These results showed that avian HEV shares antigenic epitopes in its ORF2 capsid protein with swine and human HEVs. The antigenic relatedness of avian HEV ORF2 capsid

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protein with human HEV and swine HEV provides specific factual evidence of antigenic cross-reactivity that proves there is a reasonable and substantial likelihood that antibodies will be produced from challenge by an avian HEV vaccination.

Figure 22A shows Western blot analyses of antigenic cross-reactivity of avian HEV, swine HEV, human HEV and BLSV. Figure 23 and Example 19 also illustrate the ELISA results generated from cross-reactivity of different antigens with different antisera. Figures 25A-25D show hydropathy and antigenicity plots of the truncated ORF2 proteins of avian HEV (Fig. 25A), swine HEV (Fig. 25B), Sar-55 strain of human HEV (Fig. 25C) and US2 strain of human HEV (Fig. 25D). The exemplification of the strong antigenic cross-reactivity in the specification would lead one of ordinary skill in the art to conclude that there is a significant correlation that vaccination with avian HEV will be protective against avian or mammalian HEV infection.

On page 16, lines 15-21, Applicants have further described how Schofield *et al.* generated neutralizing MAbs against the capsid protein of a human HEV (D. J. Schofield *et al.*, "Identification by phage display and characterization of two neutralizing chimpanzee monoclonal antibodies to the hepatitis E virus capsid protein," J. Virol. 74:5548-55 (2000)). The neutralizing MAbs recognized the linear epitope(s) located between amino acids 578 and 607. The region in avian HEV corresponding to this neutralizing epitope is located within the truncated ORF2 of avian HEV that reacted with human HEV and swine HEV anti-sera. In sum, there is enough proof that immunization with an avian HEV vaccine will, more likely than not, be effective against viral infection or hepatitis-splenomegaly syndrome caused by an avian or mammalian hepatitis E virus.

The successful Jennerian approach on page 488 of FIELDS VIROLOGY to the development of live attenuated viruses such as bovine parainfluenza virus type 3 and rhesus rotavirus, a vaccine candidate, cannot be ignored. The Jennerian approach uses a virus strain of mammalian or avian origin to immunize humans against a human virus that is related antigenically to the animal or avian strain. In the present application, Applicants expressly teach that the vaccine based on the avian HEV can be preferentially designed to protect against human hepatitis E through this Jennerian approach, *i.e.*, the approach taken by Edward Jenner to develop the cowpox virus vaccine useful against human smallpox (see the sentence bridging pages 23-24). There is good precedent to predict Applicants' success like Jenner's.

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There is also a well-known correlation between antigenic substances producing antibodies and a reasonable expectation of a protective, immunological reaction. The antigenicity of the avian HEV has been amply demonstrated in the specification. Based on the written disclosure and demonstration of cross-antigenicity, one of ordinary skill in the art can predict that the avian HEV would be useful and protective as a vaccine. It is clear that one of ordinary skill in the art can practice the claimed invention without undue effort.

In view of the foregoing comments together with the proffered evidence and comments of records, it is respectfully asked that the rejection of Claims 8-13 under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Examiner rejects Claim 8 under 35 U.S.C. § 112, first paragraph, for reasons set forth on pages 6 and 7 of the Office action. Without comment on the merits of this rejection but to expedite matters, Applicants have amended original Claim 8(e) (now Claim 8(d)) for the better readability thereof. It is believed that the amendment will obviate the rejection. Hence, Applicants respectfully ask that this rejection be withdrawn.

The Examiner rejects Claims 14 and 15 under 35 U.S.C. § 112, first paragraph, as failing to provide enablement for a method for inactivating or attenuating the virus by serially passing the virus through additional embryonated chicken eggs until the virus is rendered inactivated or attenuated for reasons set forth on pages 7 and 8 of the Office action. Applicants respectfully traverse this rejection but also note that they are pleased to see that the Examiner holds that the specification is enabling for the claim-recited method for propagating an avian HEV having SEQ ID NO:1 in an embryonated chicken egg. In view of the present amendment and the following comments, Applicants respectfully request reconsideration of the patentability of the rejected subject matter of Claims 14 and 15.

The present amendment makes it clear in Claim 14 that repeated passaging through eggs was not intended as a means of achieving the inactivation of the virus. One of ordinary skill in this art would have readily appreciated this obvious misstatement. (Although not noticed by the Examiner, the inadvertent, obvious error has also been corrected in Claim 9.) For the better readability of the claimed invention, the inactivation of the virus is redefined as an optional procedure after the virus has been propagated in an embryonated chicken egg. The specification on page 20, lines 17-27 thereof, provides ample support of the claimed method for inactivating

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an avian HEV through a detailed description of various art-recognized ways to inactivate the virus. The instruction in the text sufficiently enables one of ordinary skill in the art to understand what was intended by the claimed method and how to practice the claimed invention without undue experimentation.

As an example of unpredictability and undue experimentation with respect to the alternative method for attenuating the virus, the Examiner again cites the single failure of Theiler to make additional attenuated mutants of yellow fever after successfully obtaining an attenuated 17D strain of virus and adds that the genetic basis for attenuation of measles, mumps, rubella, yellow fever and vaccinia viruses is unknown. Nevertheless, Theiler's single failure in light of his earlier success and the unknown basis for attenuation of several viruses are totally irrelevant. More importantly to the enablement issue in the present case, attenuated vaccines against measles, mumps, rubella, yellow fever and vaccinia viruses have been successfully prepared and used in the past. FIELDS VIROLOGY also refers to the successful Jennerian approach on page 488 to developing live attenuated viruses such as bovine parainfluenza virus type 3 and rhesus rotavirus, which is being studied as a vaccine candidate. Indeed, one of ordinary skill in the art does not need to know the mechanism of action or the genetic basis of attenuation in order to attenuate and develop a useful viral vaccine.

The predictability factor in the enablement analysis refers to the ability of the ordinary practitioner to extrapolate the disclosed results to the claimed invention. It does not require exemplification of each and every embodiment. The predictability factor only determines if the ordinary virologist would have reasonable doubt as to the accuracy of avian HEV being attenuated by serial passage through additional embryonated chicken eggs within the context of this invention.

Vaccines are typically made by serial passage through cell cultures to achieve attenuation but avian HEV has the disadvantage that it cannot be propagated in conventional cell cultures. Since avian HEV cannot grow in the standard cell culture, the avian HEV of the present invention cannot be attenuated by standard serial passage in cell cultures. However, the exemplification in this application that avian HEV can be uniquely propagated in embryonated chicken eggs shows that the embryonated eggs, more likely than not, may be used in place of cell cultures to attenuate the avian HEV. There is a solid basis for finding that the serial passage of

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the avian HEV through additional embryonated chicken eggs would be a useful means for attenuating the avian HEV. Therefore, the specification in light of common knowledge provides sufficient guidance to one of ordinary skill in the art to be able to practice the methods of Claims 14 and 15 without undue effort.

In view of the foregoing remarks, it is respectfully requested that the rejection of Claims 14 and 15 under 35 U.S.C. § 112, first paragraph, be withdrawn and the application be allowed.

While it is hoped that this present amendment will suffice to allow the case, the Examiner is invited to contact the undersigned attorney to resolve any outstanding issues in order to put this application in proper condition for an allowance.

Accordingly, favorable treatment is respectfully urged.

Respectfully submitted,
VIRGINIA TECH INTELLECTUAL PROPERTIES, INC.

Date: June 18, 2004

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service on June 18, 2004 with sufficient postage as first class mail in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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APPENDIX

AMENDMENTS TO THE CLAIMS

Please amend the claims as follows:

1 (Previously presented). An isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand.

2 (Canceled).

3 (Currently amended). An isolated polynucleotide comprising a member selected from the group consisting of:

(a) the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand; and

(b) ~~the~~ a polynucleotide which hybridizes to ~~and which is at least 95% complementary to~~ the nucleotide sequence set forth in SEQ ID NO:1.

4 (Canceled).

5 (Canceled).

6 (Currently amended). An immunogenic composition comprising a nontoxic, physiologically acceptable carrier and a member selected from the group consisting of:

(a) an isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 [[,]] or its complementary strand; and

(b) ~~or~~ the isolated polynucleotide according to Claim 3.

7 (Canceled).

8 (Currently amended). A vaccine that protects an avian or mammalian species from viral infection or hepatitis-splenomegaly syndrome caused by an avian or mammalian hepatitis E virus comprising a nontoxic, physiologically acceptable carrier and a member selected from the group consisting of:

(a) a modified live avian hepatitis E virus, which is prepared from an isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand;

(b) an inactivated avian hepatitis E virus, which is prepared from an isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand;

(c) an attenuated avian hepatitis E virus, which is prepared from an isolated avian hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand; and

(d) ~~an antigenic subunit of avian hepatitis E virus, having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand; and~~

~~(e)~~ a polynucleotide which hybridizes to ~~and which is at least 95% complementary to~~ the nucleotide sequence set forth in SEQ ID NO:1.

9 (Original). The vaccine according to Claim 8, wherein said virus is ~~inactivated or~~ attenuated by serial passage of the virus through embryonated chicken eggs.

10 (Original). The vaccine according to Claim 8, wherein said vaccine further contains an adjuvant.

11 (Original). A method of protecting an avian or mammalian species from viral infection or hepatitis-splenomegaly syndrome caused by the avian or mammalian hepatitis E virus comprising administering an immunologically effective amount of the vaccine according to Claim 8 to an avian or mammalian species in need of protection against said infection or syndrome.

12 (Original). The method according to Claim 11, wherein the vaccine is administered to a chicken, a pig or a human.

13 (Original). The method according to Claim 11, wherein the vaccine is administered orally, intrabuccally, intranasally, transdermally or parenterally.

14 (Currently amended). A method for propagating, inactivating or attenuating a hepatitis E virus having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand comprising inoculating an embryonated chicken egg with a live, pathogenic hepatitis E virus, ~~and~~ recovering the live, pathogenic hepatitis E virus and optionally taking an additional step of inactivating the live, pathogenic virus or serially passing the pathogenic virus through additional embryonated chicken eggs until said virus is rendered ~~inactivated or~~ attenuated.

15 (Original). The method according to Claim 14, wherein the live, pathogenic hepatitis E virus is injected intravenously into the embryonated chicken egg.

16 (Canceled).

17 (Canceled).

18 (Canceled).

19 (Currently amended). A method for detecting an avian hepatitis E viral nucleic acid sequence having the nucleotide sequence set forth in SEQ ID NO:1 or its complementary strand in an avian or mammalian species comprising isolating nucleic acid from the avian or mammalian species, hybridizing the isolated nucleic acid with a suitable nucleic acid probe or oligonucleotide primer consisting of SEQ ID NO:1 or its complementary strand and ~~determining~~ detecting the presence ~~or absence~~ of a hybridized probe complex as an indication of the presence of the avian hepatitis E viral nucleic acid.

20 (Currently amended). The method according to Claim 19, wherein the isolated nucleic acid is hybridized with a radio-labeled or a non-radiolabeled nucleic acid probe ~~derived from the nucleotide sequence set forth in SEQ ID NO:1~~ or hybridized with a pair of oligonucleotide primers ~~derived from the nucleotide sequence set forth in SEQ ID NO:1~~ and further amplified in a polymerase chain reaction.